REMARKS

The undersigned wishes to thank Examiner Miller and Moran for discussing the Office Action during the recent interview. Briefly, during the interview, it was discussed that the issue raised under 35 U.S.C. 101 could be obviated by reciting that information is displayed or otherwise provided. The claims presented herein adopt that recommendation. The Petricoin and Golub documents also were discussed and that those documents do not disclose or otherwise suggest, among other things, a first and a second independent data set as disclosed and claimed in the present application, or selecting an intersection of data elements from the initial subsets, as Applicants disclose and claim.

Claims 1-111 have been cancelled without prejudice, and claims 112-220 have been added. The Abstract also has been amended as requested by the Examiner. No new matter has been added. For instance, support for the new claims appears e.g. at pages 4, 22, 31 and 45 and the original claims of the application.

It is believed the amendment to the Abstract made herein obviates formalities objection noted in the Office Action.

Claims 27, 63, and 104 were rejected under 35 U.S.C. 112, second paragraph on grounds of indefiniteness. On grounds that the phrase "data point relating to the cellular localization of components in a sample" is indefinite.

While Applicants disagree with the rejection, the new claims also do not recite the language noted in the Office Action. It is therefore believed the rejection is properly withdrawn.

Claims 1-3, 5, 8-9, 12, 17-20, 23-25, 27, 31-32, and 34-35 were rejected under 35 U.S.C §101 as being directed to non-statutory subject matter.

While Applicants also disagree with this rejection, as indicated above, independent claim 112 calls for "displaying the intersection subset on a graphical display interface on a user device" in accordance with the Examiner's recommendations.

In view thereof, reconsideration and withdrawal of the rejection are requested.

Claims 1-2, 8-9, 12, 17-20, 23-25, 27-28, 30-32, and 35 were rejected under 35 U.S.C. §102 over Petricoin, *The Lancet*, 359:572-577 ("Petricoin").

Claim 34 was rejected under 35 U.S.C. §103 over Petricoin in view of Barnhill, U.S. Patent No. 6,789,069 ("Barnhill") and/or Golub, *Science*, 286:531-537 ("Golub").

Claims 3, 5, 29, 36-38, 40, 44-45, 48, 53-56, 59-61, 63-67, 71-79, 81, 85-86, 89, 94-97, 100-102, 104-108 were rejected under 35 U.S.C. §103 over Petricoin in view of Barnhill, U.S. Patent No. 6,789,069 ("Barnhill").

For the sake of brevity, the three rejections are addressed in combination. Such a combined response is considered appropriate because, *inter alia*, each rejection relies on the Petricoin document as the sole or primary citation.

The rejection is traversed.

During the interview, the Examiners stated that as they interpreted the claim, a set of samples from, e.g., cancer patients and a set of samples from, e.g. non-cancer patients, constituted two "independent data sets." While Applicant differs with the Examiners on this point, Applicant has amended the claims to make it more clear that the invention involves performing multivariate analysis on a **first set** of samples that includes samples classified into at least two different biological states (e.g., cancer and non-cancer) and, **separately**, performing multivariate analysis on a **second set** of samples that includes samples classified into the different biological states. By doing so, the method allows one to select biomarkers common to both sets, thereby providing an internal validation of biomarkers one cannot achieve by

examining only a first set of samples. Therefore, the method assists in determining whether a biomarker actually reflects, e.g., the underlying disease or reflects a preanalytical bias, such as sex bias in the population, age bias, collection method bias, etc.

As the present application describes at page 2, lines 4-6, the "commonly accepted approach has been to pool data from multiple sources to form a combined data set and then to divide the data set into a discovery/training set and a test validation set."

That prior approach, using a single discovery data set, is what is done by Petricoin.

In contrast, Applicants' independent claim 112 calls for "providing first data from a first set of samples" and "providing second data from a second set of samples" wherein the samples show a statistically significant difference with respect to a pre-analytical variable.

Independent claims 149 and 182 also call for first and second independent discovery data sets.

Nowhere does Petricoin or any of the other cited documents teach or otherwise suggest performing classification analysis on a first set of samples including two different biological state classes (e.g., cancer and non-cancer) and then performing classification analysis on a second, independent, set of samples also including the two different biological state classes, as applicants disclose and claim.

Applicants have found their disclosed preferred methods can provide notable advantages, including accurate identification of desired biomarkers. This is discussed at page 3, first paragraph of the present application:

> The invention provides bioinformatics tools to analyze expression profiling data of samples from two or more independent sources in a way which reduces the sources of variability and biases which result in identification of false targets during the drug discovery process. In contrast to prior methods, data from multiple sources are NOT pooled together in a combined data set and then divided into a discovery-training set and a test-validation set. Instead, data from multiple sources (e.g., such as multiple different clinical trial sites) are analyzed separately and independently from the others. For each source, sufficient sample size and statistical re-sampling methods (e.g., such as bootstrap analysis) help to discover biomakers that perform well in a representative population and perform *consistently* well among different randomly selected subpopulations.

Nor does Petricoin or any of the other cited documents disclose or suggest: use of an intersection subset of data elements as Applicants disclose and claim, i.e.

"selecting an intersection subset of data elements from the first and second subsets, wherein each data element in the intersection subset is a member of both of the first and second subsets" as recited in Applicants' independent claim 112;

"a third computer readable program providing instructions for selecting an intersection subset of data elements from the initial subsets, wherein each data element in the intersection subset is a member of a majority of the initial subsets" as recited in Applicants' independent claim 149; and

"executing computer readable program code providing instructions for selecting an intersection subset of data elements from the initial subsets, wherein each data element in the intersection subset is a member of a majority of the initial subsets" as recited in Applicants' independent claim 182.

See also the discussion at pages 44-45 of the application.

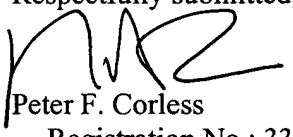
Golub fails to remedy such deficiencies of the Petricoin document. Golub merely reports that prediction strength was low from laboratories using different collection protocols, see p. 533, first column. Notably, Golub also reports that sample preparations should be standardized, thereby teaching away from Applicants' method where independent discovery data sets may be collected from different locations or from using different collection protocols. Nowhere does Golub disclose or suggest "selecting an intersection subset of data elements from the first and second subsets" as Applicants claim.

Barnhill also does not disclose or suggest use of first and second independent discovery data sets as Applicants claim. Barnhill also does not suggest "selecting an intersection subset of data elements from the first and second subsets" as Applicants claim.

Reconsideration and withdrawal of the rejections are therefore requested.

It is believed that the application is in condition for immediate allowance, which action is earnestly solicited.

Respectfully submitted,



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